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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

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PAPER NUMBER

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6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/091,608

Applicant(s)

Bebbington et al.

Examiner

Peter Brunovskis

Group Art Unit

1632



☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-52 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-5 and 11-16 is/are rejected.

☒ Claim(s) 6-10 and 17-52 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Priority

Applicant is advised of possible benefits under 35 U.S.C. 119(a)-(d), wherein an application for patent filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country. Although a certified copy of GB 9526131.9 has been filed, priority to this application was not claimed in the declaration.

Specification

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) Title of the Invention.
- (b) Cross-References to Related Applications.
- © Statement Regarding Federally Sponsored Research or Development.
- (d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
- (e) Background of the Invention.
 - 1. Field of the Invention.
 - 2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (f) Brief Summary of the Invention.
- (g) Brief Description of the Several Views of the Drawing(s).
- (h) Detailed Description of the Invention.

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- (i) Claim or Claims (commencing on a separate sheet).
- (j) Abstract of the Disclosure (commencing on a separate sheet).
- (k) Drawings.
- (l) Sequence Listing (see 37 CFR 1.821-1.825).

There are no section headings (as listed above) for (e), (f), (g), and (h). Also, Figures 2a, 2b, 2c are not described on p. 13 of the specification.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claims 6-10, 17-52 are objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim should refer to other claims in the alternative only (e.g. cl. 17-52), and/or, cannot depend from any other multiple dependent claim (e.g. cl. 6-10). See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim 3 objected to because of the following informalities: Claim 3 recites the term "and/or" in line 2. Also, in claim 5, line 2, "of" should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-3 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) is incomplete for failing recite method steps that relate back to the preamble which is drawn to "[a] method of activating a cell" as a result of ...an interaction between "said first cell and a molecule". This method claim recites no active process steps and does not recite how the "DNA delivery system" serves to "activate" a cell or to define its relationship to "extracellular interaction" or "a molecule associate with a second target cell".

Claims 1 and 11 (and dependent claims) are vague in their recitation of "one type of extracellular interaction" since it is unclear *which type* of interaction is being referred to. Also, in claim 1, "molecule associated with" is indefinite since it is unclear what the nature of the "association" is between the "molecule" and the "second target cell".

Claim 1 (and dependent claims) recites the limitation "said first cell" in lines 2 and 3 and claims 1 and 12 recite the limitation "said cytoplasmic components" (cl. 1, lines 6, 7; cl. 11, line 5). There is insufficient antecedent bases for these limitations in the claims. Furthermore it is unclear what "second target cell" refers to since there is no --first-- target cell established.

Claim 1 (and dependent claims) is rendered indefinite by its recitation of "provided with" and "comprising two or more" (line 5) since it is unclear *how* the "DNA delivery system" is "provided" to "said first cell" or whether "comprising" in line 5 refers to the cells, the DNA delivery system, or the receptors

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Claims 1, 11, and 12 (and dependent claims) are rendered indefinite by their recitation of "not naturally linked" since it is unclear how the method step of claim 1 relates to the definition of "not naturally linked" as recited on p. 3. Specifically, the method steps do not make clear whether the cytoplasmic [signalling] components referred to represent cytoplasmic signalling components which *in nature* are not connected to each other on a single polypeptide chain, but which *are* connected this way in the embodiments covered by these claims or whether the signalling components not connected in nature *are also not linked* together in the embodiments of the recited claims.

Claim 1 (and dependent claims) is rendered indefinite by the term "at least one" since it is not clear whether "one" refers to "one" of the "cytoplasmic components" or a part of a "recombinant chimeric receptor" that is not a cytoplasmic component.

Claims 1 and 11-16 (and dependent claims) are rendered indefinite by their recitation of "derived from" since it is unclear how "derived from" is defined or what the structural relationship is between the components to which the claims are drawn..

Claims 2, 3, 11, 12, 13, 14 (and dependent claims) are rendered indefinite by their recitation of "capable of" since the metes and bounds of "capable of" are unclear in the context of these claims (e.g. capable of under what circumstances?). Furthermore, claim 2 is indefinite in its recitation of "capable of acting together cooperatively" since the nature of the "cooperativ[ity]" is unclear and it is unclear whether the invention requires that the components actually "act" together.

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Claim 3 recites the limitation "said one or more chimeric receptors" in line 3 and "the binding component" in lines 3 and 4. There is insufficient antecedent bases for these limitations in the claim.

Claim 3 is rendered indefinite by its recitation of "additionally codes for signal peptide, binding and/or transmembrane components" since it implies the addition of an "extra layer" of said components since the "chimeric receptors" referred to claims 1 or 2 would implicitly contain such domains, otherwise they wouldn't be receptors. Also it is unclear what the structural relationship is between the "DNA" and the receptors or what the meaning of "capable of" is in this context.

Claims 4 and 5 is rendered indefinite by its recitation of "part of the binding component" (lines 2 and 3) since it is unclear what encompasses the metes and bounds of "part", since a single amino acid (or functional group) can constitute a "part of a binding component". Also, it is not clear whether the "single DNA" recited in line 3 of claim 4 applies individually or collectively to the recited "components" (e.g. signal peptide, transmembrane, cytoplasmic...etc.).

Claim 4 recites the limitation "transmembrane" in line 2. There is insufficient antecedent basis for this limitation in the claim. Moreover, it is unclear whether the "transmembrane" recited comprises "signalling components".

Claim 5 is rendered indefinite by its recitation "wherein each cytoplasmic signalling component is coded for by a separate DNA sequence" since each cytoplasmic signalling

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component, independent of whether it is on a separate DNA molecule, will *code for* a separate DNA coding sequence. Also it is unclear which "DNA sequence" in line 3 is being referred to.

Claim 11 is indefinite since it is unclear whether the DNA coding for the recombinant chimeric receptor also encodes the cytoplasmic signalling components or whether the components are perhaps "associated with" the carrier and/or DNA.

Claims 11 and 12 are vague in their recitation, "in association with" since it is unclear what the nature of the "association" is between the "DNA" and the "carrier".

Claim 12 recites the limitation "the same one type of extracellular interaction" in line 3. There is insufficient antecedent basis for this limitation in the claim. Further, it is unclear *which type* of extracellular interaction is being referred to.

Claim 14 is rendered indefinite by its recitation of "part of a [the] binding component" (lines 4 and lines 12, 13) since it is unclear what part is being referred to or what encompasses the metes and bounds of this limitation, since a single amino acid (or functional group) can constitute a "part of a binding component" and since there is no limitation recited requiring *both* binding components to reconstitute a binding event wherein either component alone is "[un]capable of recognising a cell surface molecule" by itself.

Claims 14-16 are rendered indefinite by their recitation of "a second separate DNA" and by "a separate third and fourth DNA" in claim 16 since it is unclear whether "separate" refers to separate DNAs on the *same* nucleic acid molecule or *different* nucleic acid molecules.

Additionally, in claim 14 it is unclear whether "together" line 14 refers to the binding component

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parts alone or the product of the second separate DNA or even the DNA delivery system as a whole.

Claim 16 is extremely confusing. First, in claim 16 it is not clear how a "separate third and fourth DNA" (in line 14) can encode a "further part of the binding component ii) encoded "by said first and second separate DNA, respectively". Moreover, in claim 16 it is not clear *which* of the DNAs constitute the "third and fourth" DNAs (line 14), the "first and second" (line 16), the "first and third" DNAs (line 18), the "second and fourth" DNAs (line 19) or what their relationship is individually or in pairs to the "recognising a cell surface molecule on a target cell" (lines 19 and 20). Also it is unclear what "together" (line 18) and "each" (line 19) refer to. Claim 16 is further indefinite in its recitation of "capable of recognising a cell surface molecule" since the metes and bounds of this phrase cannot be accurately determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Operably linked promoters considered critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification teaches that

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practicing the invention requires expression of the chimeric receptors, which would require a promoter operably linked to receptor genes. The specification does not teach how to use the DNAs of the claimed invention lacking operably linked promoters facilitating gene expression resulting in production of receptor polypeptides. The claims should be amended to recite operable linkage of a promoter to the recited coding sequences.

Claims 1-5 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use in cultured cells of the embodiments recited in Examples 2-6 of the specification (pp. 24-36), does not reasonably provide enablement for the broad range of embodiments embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining enablement are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation.... Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount or direction or guidance presented, the presence or absence of working

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examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Claims 1-5 and 11-16 are poorly written and extremely broad in scope. Although the specification describes several DNA constructs shown to be useful in inducing IL-2 production coincident with stimulation of appropriate cytolytic T cells subsets, it is unclear whether other chimeric receptors broadly embraced by the instant claims containing two or more cytoplasmic signalling components would be a priori functional. Any construction would have to be evaluated on a case by case basis. There is no guidance teaching one of ordinary skill in the art how to use defective embodiments, nor does the specification provide any expectation of success that a given DNA construction would be functional, nor are there any specific claims made to any of the *specific embodiments* that have been provided as working examples. There is no precedent for the fact that simple *colocalization of two or cytoplasmic signalling components* in the manner proscribed therein would be predictably sufficient to promote or mimic the sort of "activation" that is characteristically seen in cases wherein receptors are activated and co-stimulated through multiple ligand/receptor interactions.

The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific

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laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In the absence of further guidance and examples, it is unclear whether one of ordinary skill in the art can make and use the broad range of embodiments embraced by the instant claims without undue experimentation, particularly since there is no guidance teaching one of ordinary skill in the art how to use defective embodiments, nor does the specification provide any expectation of success that a given DNA construction would work. It is further noted that the specification does not provide an enabling disclosure for the pharmaceutical use of the DNA delivery system of the claimed invention for either *in vivo* or *ex vivo* gene therapy.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the claimed products and methods. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples in the specification, and the amount of experimentation necessary.

Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-16, appear to be drawn to chimeric receptors containing binding components unable to facilitate interaction with a target molecule on their own, but only in the presence of

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another. The specification does not teach how to make such embodiments, nor does it provide working examples or teach how to use such embodiments. Claim 16 is extremely confusing to follow, but it appears to be drawn to a combination system comprising two separate pairs of expression vectors wherein each pair comprises two chimeric receptors capable of reconstituting binding to a molecule on the surface of a cell. Although Table 1 lists various combinations of two-chimeric receptor examples, the specification fails to give the criteria used to establish which component parts should be combined together in such pairs wherein the binding component parts "together are capable of recognising a cell surface molecule on a target cell".

An adequate written description of the DNAs of claims 14-16 requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is not sufficient to provide a disclosure of no more than a simple claim to a DNA carrying certain structural properties. When one is unable to envision the detailed constitution of a complex chemical compound having particular functional limitations, particularly those recited in claims 14-16, so as to distinguish it from other materials, as well as a methodology for obtaining and determining the specific make-up of the components therein, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated and tested. An adequate description of the methods requires an adequate and clear description of the specific objectives and materials which provide the means for practicing the invention.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371 of this title before the invention thereof by the applicant for patent.

Note: the claims are poorly written and difficult to interpret; therefore, for purposes of prior art, the broadly written claims are broadly interpreted.

Claims 1-5 and 11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Capon et al. (US 5,359,046).

Capon et al. disclose methods for activating a cell wherein a cell is provided with a DNA delivery system comprising DNA coding for a recombinant chimeric receptor comprising two or more different cytoplasmic signalling components wherein the cytoplasmic components of the recombinant chimeric receptor and the signalling components of the cell (encoded for by a separate chromosomal DNA) are not naturally linked (see col. 52, cl. 14).

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Claims 1-5, 11-13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated or clearly anticipated by Feng et al. (J. Biol. Chem., 270:24237-24245, 1995).

Feng et al. discloses a DNA delivery/cell activation system comprising cotransfection (into cells) of two chimeric TGF- β receptor constructs each bearing a different not naturally linked cytoplasmic domain derived from a membrane spanning polypeptide wherein the two recombinant chimeric receptors are each capable of the same one type of extracellular interaction with a molecule (TGF- β) associated with (or present on) cells. Each of the DNAs contains a different extracellular binding component that is capable of recognizing TGF- β ligand on a cell surface either alone or together with the other (see Fig. 2, p. 24240 and Fig. 4, p. 24241). It is further noted that since the DNAs encode receptors, they inherently possess a signal peptide component and spacer regions between the above domains (or components).

Claims 1-5, 11-13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated or clearly anticipated by Nelson et al. (Nature, 369:333-336, 1994).

Nelson et al. describe a DNA delivery/cell activation system comprising cotransfection (into cells) of chimeric receptors each bearing an extracellular region (or binding component) from either c-kit or GM-CSFR (that are each capable of the same one type of extracellular interaction with a molecule [i.e. c-kit or IL-2] and which are together capable of recognising a c-kit or IL-2 ligands associated with T-cells) which is fused in a non natural linkage to the cytoplasmic domains (β and γ chains) of the membrane spanning IL-2 receptor wherein treatment

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with SCF ligand (for c-kit) or IL-2 was found to result in heterodimerization of the cytoplasmic β and γ chains, necessary and sufficient for generating the signal for T-cell activation. It is further noted that since the DNAs encode receptors, they inherently possess a signal peptide component and spacer regions between the above domains (or components).

Claims 1-5, and 11-15 are rejected under 35 U.S.C. 102(e) as being anticipated or clearly anticipated by Roberts (US 5,712,149).

Roberts discloses a DNA delivery/cell activation system comprising chimeric receptors and/or cells comprising in reading frame a signal peptide component, an extracellular binding component (e.g. single chain antibody, see cl. 5) capable of recognizing a cell surface molecule, a transmembrane component, a non-naturally linked cytoplasmic signalling component of CD2 or CD28 (see col. 31, cl. 1) and/or an additional non-naturally linked cytoplasmic signalling component (see Fig. 1D and col. 32, cl. 12) wherein the cytoplasmic signalling components from CD2 and CD28 and/or some members of the group recited in cl. 12 are derived from membrane spanning polypeptides. Roberts further discloses cells comprising one or more of the above DNAs (see col. 33, cl. 15 and cl. 20).

Claims 1-5, 11-16 are rejected under 35 U.S.C. 102(e) as being anticipated or clearly anticipated by Seed et al. (US 5,912,170).

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Seed et al. discloses a DNA delivery/cell activation system comprising chimeric receptors and/or cells comprising in reading frame a signal peptide component, at least two extracellular binding components capable of recognizing a cell surface molecule (see cl. 9, , a transmembrane component, a non-naturally linked cytoplasmic signalling component, for example, a portion of a Src family protein-tyrosine kinase (see col. 42, cl. 4) and/or a portion derived from the membrane spanning protein, CD28 (see cl. 1, 32, and 62, for example). Seed further discloses cells comprising at least three chimeric receptors of the above DNAs (see col. 41, cl. 4) wherein the extracellular components or the cytoplasmic signalling components, comprising kinase domains, each contain binding component parts "capable of recognising a cell surface molecule on a target cell".

Claims 1-5, 11-16 are rejected under 35 U.S.C. 102(a) as being anticipated or clearly anticipated by Capon et al. (WO 96/24671).

Capon et al. discloses a DNA delivery/cell activation system comprising cells and/or multiple chimeric, multispecific receptors encoded by separate DNAs comprising in reading frame, a signal peptide component, at least two extracellular binding components capable of recognizing a cell surface molecule, a transmembrane component, and two non-naturally linked cytoplasmic signalling components, including a cytoplasmic effector function signalling domain and a cytoplasmic proliferation signalling domains derived from membrane spanning polypeptides (see p. 3, lines 17-28 and claims, pp. 92-109; for example, cl. 17, 18, 20, 25, 27, 30, and 47-50).

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Conclusion

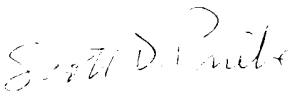
Since there is no special technical feature in the first invention of independent claim 1 shared by the other recited inventions, which considered as a whole, define a contribution over the prior art, future examination of amended claims will accordingly be subject to restriction practice, including species election.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, Ph.D. can be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632


SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER